Health Literacy, Antiretroviral Adherence, and HIV-RNA Suppression

A Longitudinal Perspective

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BACKGROUND: Low health literacy has been associated with worse adherence to antiretroviral therapy (ART) and higher HIV-RNA levels, but these relationships have not been evaluated in longitudinal analyses.

METHODS: We evaluated literacy using the Rapid Estimate of Adult Literacy in Medicine (REALM) ($\leq$6th grade, 7th to 8th grade, $\geq$9th grade) in the HIV-Alcohol Longitudinal Cohort study of HIV-infected persons with a history of alcohol problems, conducted from 1997 to 2001. We tested HIV-RNA levels and administered a standardized questionnaire regarding demographics, substance use, receipt of ART, and adherence with ART, every 6 months for up to 7 occasions. Among the 235 subjects on ART, we investigated the relationship between literacy and 2 outcomes: 100% 3-day self-reported adherence and HIV-RNA suppression (<500 copies).

RESULTS: Subjects' literacy levels were the following: 14% $\leq$6th grade, 29% 7th to 8th grade, and 57% $\geq$9th grade. In 66% of the observations (478/725), subjects reported 100% 3-day adherence with ART. Of the 685 HIV-RNA assays from these subjects, 62% had <500 copies. In unadjusted analyses, subjects with the lowest literacy level ($\leq$6th grade) had a higher odds of adherence (odds ratio [OR] 2.23, 95% confidence interval 1.15 to 4.30) and HIV-RNA suppression (OR 2.01, 95% confidence interval 1.03 to 3.90) compared with those with $\geq$9th grade literacy. This trend persisted but was no longer statistically significant in adjusted models of adherence (AOR 1.93, 95% confidence interval 0.86 to 4.31) and HIV-RNA suppression (AOR 1.70, 95% confidence interval 0.79 to 3.65).

CONCLUSION: Contrary to our hypothesis, low literacy was not associated with a lower odds of adherence or virologic suppression in this longitudinal analysis of HIV-infected patients with a history of alcohol problems. Indeed, trends in these data suggest the possibility that low literacy may be associated with a higher odds of adherence and virologic suppression. These counterintuitive findings underscore the need to pursue a fuller understanding of the mechanisms by which literacy affects health outcomes.

H ealth literacy has emerged as a cross-cutting priority to improve the quality of health and health care in America.[1–4] Medical and public health literature highlight the high reading demands made on people who are often in need of important health information.[5] In addition, there is a growing body of literature indicating that people with limited health literacy have worse health status.[6,7]

Health literacy has been defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" and includes aspects of basic literacy as well as vision, cognition, hearing, communication, navigation, and culture.[3] Various mechanisms linking low health literacy to worse health outcomes have been proposed.[8] However, as most reports have presented cross-sectional analyses, a mechanistic understanding of how low health literacy might actually cause worse health outcomes has remained elusive.[9,10] One prominent theory maintains that adherence to medication regimens is lower in patients with low health literacy.[8] An excellent model to examine such a mechanism is in patients with HIV as health outcomes are likely to be particularly sensitive to variation in adherence.[11]

While many studies have investigated determinants of antiretroviral therapy (ART) adherence,[12–22] few authors have examined the role of health literacy in ART adherence among patients with HIV. The goal of this paper is to evaluate the role of literacy in longitudinal analyses of adherence and viral load suppression among patients with HIV. We hypothesized that low health literacy would be associated with worse adherence and less frequent viral load suppression.

METHODS

Study Population

This is a longitudinal analysis evaluating data including literacy status, ART adherence, HIV-RNA level, and addiction severity from a prospective cohort of HIV-infected patients with a history of alcohol problems. Between July 1997 and August 2001, we recruited HIV-infected subjects with a history of alcohol problems in the following manner: Boston Medical Center HIV Diagnostic Evaluation Unit 56%; posted flyers 16%; Boston Medical Center Primary Care Clinic 13%; respite facility for homeless persons 5%; methadone clinic 4%; subject referrals 4%; and Beth Israel Deaconess Medical Center 2%. All potential subjects who gave 2 or more positive responses to the CAGE questionnaire (Cut down, Annoyed, Guilty, Eye-opener), a screening test for lifetime alcohol problems, were eligible.[23–25] In addition, potential subjects were eligible if an attending physician made a specific diagnosis of alcohol abuse or dependence.[26,27] Other entry criteria included the following: fluency in English or Spanish; Mini-Mental State Examination score $\geq$21; and no plans to move from the Boston area within 2 years.[28] We screened 474 subjects at these various sites. There were 422 eligible subjects, of whom 349 (82.5%) provided informed consent and agreed to participate in the original study.[29]

A nested randomized-controlled intervention trial to promote ART adherence was conducted with 150 of the 349 subjects, as depicted in Figure 1. Intervention subjects had:

(1) assessment and discussion of alcohol use based on stage of readiness for behavioral change; (2) use of a watch that served as a medication timer device, a practical aid to improving adherence; (3) counseling to promote perceived efficacy of medications; and (4) individualized HIV counseling and exploration of ways to tailor medication use to specific circumstances. Subjects randomized to the intervention group were scheduled for an initial 60-minute individual appointment (within 2 weeks after randomization), a follow-up home visit within the first 3 weeks, and 2 subsequent 15- to 30-minute appointments at 1 and 3 months with the nurse interventionist who delivered the adherence enhancement intervention.[30,31] In the analysis for this study, appropriate adjustments were made to account for trial status. The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study.

For the current analyses, health literacy is the primary independent variable of interest. Thus, subjects were excluded from the analysis if they did not complete the literacy assessment ($n=11$) or if they conducted the research interview in Spanish ($n=23$), as the Rapid Estimate of Adult Literacy in Medicine (REALM) is an English test.[32] In addition, subjects were excluded if they were not on ART ($n=80$). Consequently, the final cohort for this analysis included 235 subjects, as depicted in Figure 1. If a subject began ART during the period of observation, only data collected after that point were included.

Data Collection

After obtaining informed consent, a research associate interviewed subjects using a standardized instrument to ascertain baseline information. We attempted to obtain CD4 cell counts and HIV-RNA levels on all subjects. Laboratory tests performed within 6 months of the interview as part of clinical care were recorded. If not available through routine clinical care, blood samples were obtained and tested for CD4 cell count and HIV-RNA using the Boston Medical Center Clinical Laboratory. Research interviews and data collection were conducted every 6 months for up to 7 occasions.
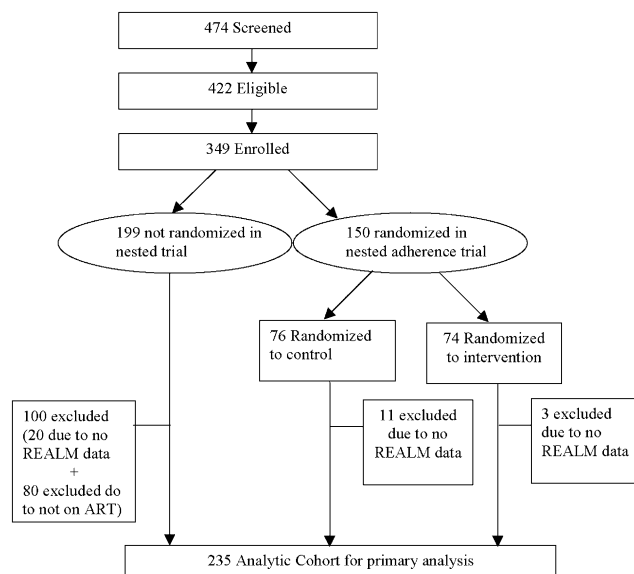

FIGURE 1. Sampling cascade for the analytic cohort.

Outcome Variables

The outcome variables of interest were (1) 3-day ART adherence (100% adherent vs $<100\%$ adherent) and (2) viral load suppression (<500 vs ≥ 500 copies/mL). Adherence was determined with the AIDS Clinical Trials Group Adherence Instrument, a self-reported questionnaire that was modified to evaluate 3-day, as opposed to 2-day, ART adherence.[33] Patients reported the names of the antiretroviral medications, as well as the number of doses and the total number of pills prescribed daily. We defined adherence as a dichotomous variable, in which patients who were $<100\%$ adherent during the previous 3 days were considered nonadherent.[12,30] Measurement of HIV-RNA was performed using branched-chain DNA techniques.[34] The threshold for detection at the time of the study was 500 copies/mL; viral load suppression was defined as having an undetectable HIV-RNA. In secondary analyses, we used 30-day self-reported ART adherence ($\geq 95\%$ adherent vs $<95\%$ adherent) as an alternate measure.

Primary Independent Variables

Our measure for health literacy was the 66-word REALM.[32] This is a 2 to 3-minute English test of medically relevant vocabulary. The REALM is a valid test of word pronunciation and has been shown to correlate well with tests that evaluate a range of literacy skills.[35] Three categories of literacy were defined based on the REALM: literacy levels of 6th grade and below (REALM score 0 to 44), 7th to 8th grades (REALM score 45 to 60), and 9th grade and above (REALM score 61 to 66).

Other Independent Variables

Other specific variables assessed included: gender, age, race (black, white, or other—the latter subjects were mostly Hispanic), severity of alcohol and drug dependence as measured by the Addiction Severity Index (ASI alcohol and ASI drug),[36] drank to intoxication in the past 30 days, injected drugs in the past 6 months, level of education, complexity of medication regimen, homelessness, and randomization group. Level of education was used as a dichotomous variable representing whether a subject had a high school diploma or general equivalency degree (GED) versus neither. The complexity of the medication regimen was categorized as low (2 to 4 doses/d), moderate (5 to 6 doses/d), or high (7 to 10 doses/d). Homelessness was defined as having spent at least 1 night either on the street or in a shelter in the 6 months before the interview.[37]

Analysis

Bivariate analyses of baseline data were performed to assess the associations between various subject characteristics and literacy. Subject characteristics were compared across literacy groups using the χ^2 test for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. Separate longitudinal logistic regression models were constructed to examine the association between literacy and each outcome (ART adherence and HIV-RNA suppression) over time. A generalized estimating equations (GEE) approach using an independence working correlation matrix was used to account for correlation due to analyzing repeated measures from the same subject over time, and empirical standard errors were used for all analyses.[38] Multivariable analyses were conducted in the

following sequence: first, gender, race, age, education, drank to intoxication in the past 30 days, injected drugs in the past 6 months, homelessness, and randomization group were entered as covariates; then, the complexity of the medication regimen was added to the model. Models examining HIV-RNA suppression also adjusted for current ART adherence. In addition, we conducted 2 sensitivity analyses to evaluate the stability of our findings for HIV RNA suppression. First, the number of observations included in the analysis was expanded to include instances of discontinuation, i.e., observations where a subject who had been on ART was no longer in receipt of ART. Then, we expanded the analytic cohort to include subjects who had a clinical indication for ART but were not in receipt of ART. All analyses were carried out using SAS (SAS Version 8.2, SAS Institute Inc., Cary, NC).

RESULTS

A total of 235 subjects contributing 725 observations (average 3.1 observations/subject) were included in the current analyses. The distribution of literacy was: 14% $\leq$ 6th grade, 29% 7th to 8th grade, and 57% $\geq$ 9th grade. In bivariate analyses, higher level of education and being white were associated with higher literacy. Baseline subject characteristics are described in Table 1.

Adherence

Among the 725 observations, 100% 3-day adherence was recorded in 478 (66%). In an unadjusted analysis, low literacy was associated with an increased odds of adherence (OR 2.23 for low vs high literacy level, 95% confidence interval [CI] 1.15 to 4.30). Although not statistically significant, in longitudinal logistic regression models (Table 2), the inverse trend remained between literacy and the odds of adherence. Factors

negatively associated with adherence in both Adherence Model 1 and Adherence Model 2 (which includes the complexity of the regimen) were having drunk to intoxication in the past 30 days (Model 2: AOR 0.32, 95% CI 0.21 to 0.48) and injected drugs in the past 6 months (Model 2: AOR 0.26, 95% CI 0.15 to 0.4). Having a less complex medication regimen was associated with a higher odds of adherence (AOR 1.96 for $\leq$ 4 doses/d compared with 7 to 10 doses/d; 95% CI 1.08 to 3.58). All findings for 30-day adherence were consistent with the 3-day adherence results.

HIV-RNA Suppression

Among the 685 HIV-RNA tests, suppression was recorded in 422 (62%). In an unadjusted analysis, the odds of HIV-RNA suppression was higher for those with low literacy compared with those with high literacy (OR 2.01 for low vs high literacy level, 95% CI 1.03 to 3.90). Although not statistically significant, in longitudinal logistic regression models (Table 3), the inverse trend remained between literacy and the odds of HIV-RNA suppression. Medication adherence was the only variable that was consistently associated with HIV-RNA suppression (Model 3: AOR 1.80; 95% CI 1.20 to 2.69).

Sensitivity Analysis

In the first sensitivity analysis, we added 101 observations (subjects who had been on ART but who were off ART at a subsequent study visit). In the second sensitivity analysis, we further expanded the analytic cohort to include all observations from subjects for whom ART was clinically indicated (CD4 count $\leq$ 350). This resulted in a sample of 266 subjects with 879 observations, an increase of 31 subjects and 53 observations. The analyses conducted on these expanded

Table 1. Characteristics of Subjects in the Analytic Dataset: Members of the HIV-ALC (HIV-Infected Persons with a History of Alcohol Problems) with a Clinical Indication for Antiretroviral Therapy (N = 266)

Characteristics, N (%)	$\leq$ 6th grade: 32 (14)	7th to 8th grade: 69 (29)	$\geq$ 9th grade: 134 (57)	Total: 235
Age in y (median [IQR])	41 [7]	42 [12]	42 [9]	42 [9]
Female	7 (22)	14 (20)	28 (21)	49 (21)
Ethnicity				
Black	**24 (75)**	**40 (58)**	**41 (32)**	105 (45)
White	**2 (6)**	**15 (22)**	**73 (54)**	90 (38)
Other	**6 (19)**	**14 (20)**	**20 (15)**	40 (17)
Homeless, y	7 (22)	24 (35)	24 (18)	55 (23)
High school graduate or equivalent degree, y	**6 (19)**	**43 (62)**	**100 (75)**	149 (63)
Nested adherence trial status				
Not in nested trial	13 (41)	23 (33)	63 (47)	99 (42)
Intervention subject in nested trial	6 (19)	24 (35)	41 (31)	71 (30)
Control subject in nested trial	13 (41)	22 (32)	30 (22)	65 (28)
Viral load suppressed at baseline visit, y	20 (63)	37 (58)	78 (61)	135 (60)
Alcohol consumption (median drinks/d [IQR])	4 [4]	6 [19]	5 [6]	6 [9]
Drank to intoxication in the past 30 d	6 (19)	24 (35)	47 (35)	77 (33)
Injected drugs in the past 6 mo	2 (6)	11 (16)	31 (23)	44 (19)
Mean ASI alcohol score (median [IQR])	0.1 [0.3]	0.1 [0.3]	0.1 [0.3]	0.1 [0.3]
Mean ASI drug score (median [IQR])	0.1 [0.2]	0.1 [0.2]	0.1 [0.2]	0.1 [0.2]
100% 3-d adherence at baseline	22 (69)	43 (63)	83 (62)	148 (64)
Complexity of ART regimen at baseline				
2 to 4 doses/d	18 (56)	39 (57)	58 (44)	115 (49)
5 to 6 doses/d	7 (22)	22 (32)	49 (37)	78 (33)
7 to 10 doses/d	7 (22)	7 (10)	26 (20)	40 (17)

P < .05 indicated by bold text.
ALC, alcohol longitudinal cohort; ART, antiretroviral therapy; ASI, addiction severity index; IQR, interquartile range.

Table 2. Longitudinal Relationship Between Literacy and ART Adherence

Literacy Level	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)	
		Model 1[*]	Model 2[†]
≤ 6th grade	**2.23 (1.15 to 4.30)**	1.90 (0.84 to 4.30)	1.93 (0.86 to 4.31)
7th to 8th grade	1.26 (0.76 to 2.08)	1.33 (0.79 to 2.24)	1.29 (0.77 to 2.19)
≥ 9th grade	1	1	1

[*]*Model 1 includes: gender, age, education, randomization group, ethnicity, homeless status, drank to intoxication in the past 30 days, and injected drugs in the past 6 months.*
[†]*Model 2 includes: model 1 (gender, age, education, randomization group, ethnicity, homeless status, drank to intoxication in the past 30 days, injected drugs in the past 6 months)+complexity of regimen.*
P<.05 indicated by bold text.
CI, confidence interval.

samples produced results that were similar to the findings from the primary analyses.

DISCUSSION

We evaluated the role of health literacy in ART adherence and HIV-RNA suppression in a 36-month prospective cohort study of HIV-infected patients with a history of alcohol problems. Contrary to our hypotheses, in unadjusted analyses, the odds of ART adherence and HIV-RNA suppression were higher in those with lower literacy. Such trends were noted even after adjusting for gender, age, education, ethnicity, homeless status, drinking to intoxication in the past 30 days, injecting drugs in the past 6 months, participation in an adherence-promoting intervention, and the complexity of the medication regimen, although in adjusted models these findings were not statistically significant.

Our findings run counter to a common hypothesis in the health literacy literature.[39] Indeed, the Institute of Medicine report on health literacy is called "Health Literacy: A Prescription to End Confusion," evoking the importance of medication adherence as a link between low literacy and worse health outcomes.[3] However, evidence about the effects of health literacy on adherence has been mixed. The Agency for Healthcare Research and Quality evidence report on Literacy and Health Outcomes identified 3 studies evaluating the relationship between literacy and medication adherence and 2 of these did not support such an association.[7,20,40,41] Two additional studies have subsequently reported the association between low literacy and low adherence to preoperative medication instructions[42] and medications for cardiovascular diseases.[43]

The 1 prior longitudinal evaluation of health literacy in a cohort of HIV-infected subjects focused exclusively on adherence: Golin et al.[44] followed patients starting on a new ART regimen for 48 weeks. In their cohort, low health literacy was associated with poor ART knowledge 8 weeks after initiation of an ART regimen; however, at 48 weeks there was no association between literacy and adherence.[20] This suggests that low health literacy may be a barrier to adherence early in the course of treatment, but that familiarity with a stable care plan could mitigate such an influence over time.

In a series of cross-sectional reports on 3 cohorts of patients with HIV in Atlanta, Georgia, Kalichman et al.[40,45–47] reported the association between low health literacy and a lower level of knowledge about HIV, worse ART adherence, lower CD4 cell counts, and higher viral loads. However, Wolf et al. reported no association between health literacy and ART adherence in a cohort of patients in a Southern U.S. HIV clinic, and van Servellen et al. described no association between health literacy and ART adherence in the setting of an intervention program for Latino men and women.[48–50]

Why might low literate patients in our study have been more adherent to ART and have better HIV-RNA suppression than those with higher literacy? The current cohort was different from previously analyzed populations in important ways. Unlike patients in the study by Golin et al., subjects in the current study were not recruited at the time of ART initiation. Whereas Kalichman et al. recruited subjects from community outreach venues, the current cohort was recruited in medical settings among people with alcohol problems. Possibly, the resilience required for low literate subjects to access care and participate in this longitudinal study resulted in a

Table 3. Longitudinal Relationship Between Literacy and HIV-RNA Suppression

Literacy Level	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)		
		Model 1[*]	Model 2[†]	Model 3[‡]
6th grade	**2.01 (1.03,3.90)**	1.85 (0.87,3.94)	1.72 (0.81,3.69)	1.70 (0.79,3.65)
7th to 8th grade	1.28 (0.79,2.09)	1.30 (0.77,2.20)	1.28 (0.75,2.16)	1.29 (0.77,2.18)
≥ 9th grade	1		1	1

[*]*Model 1 includes: gender, age, education, randomization group, ethnicity, homeless status, drank to intoxication in the past 30 days, and injected drugs in the past 6 months.*
[†]*Model 2 includes: Model 1 (gender, age, education, randomization group, ethnicity, homeless status, drank to intoxication in the past 30 days, and injected drugs in the past 6 months)+medication adherence.*
[‡]*Model 3 includes: Model 2 (gender, age, education, randomization group, ethnicity, homeless status, drank to intoxication in the past 30 days, and injected drugs in the past 6 months, and medication adherence)+complexity of regimen.*
P<.05 indicated by bold text.
CI, confidence interval.

selection bias toward low literate subjects with higher levels of adherence. While this is a possible contributing factor, it is important to note that other variables in the analyses operated as expected (e.g., a less complex drug regimen was associated with better adherence, and having drunk to intoxication in the past 30 days was associated with worse adherence).[17,19,51]

It is also possible that patients with low literacy may have difficulty acquiring the self-management skills required for a new drug regimen, but once in a therapeutic steady state may actually follow directions more readily than those with higher literacy. Low literacy has been linked with low self-efficacy, which has been identified as a risk factor for worse adherence.[52] However, it is also possible that patients with higher levels of self-management efficacy may be predisposed to worse adherence, as may have been the case for the higher literacy subjects in this study.[53,54] An example of how this could occur would be if higher literacy subjects felt they could adjust medications due to perceived side effects without conferring with a health provider. Future analyses to evaluate potential mediators such as aspects of self-efficacy, knowledge, and understanding will be important to elucidate the causal pathways for the varied findings on the association between literacy and adherence.

This study has several limitations. First, adherence was evaluated by self-report. Although self-reported adherence typically correlates with other measures of adherence, other forms of adherence evaluations were not conducted.[55,56] An additional adherence variable (30-day self-report) was evaluated in this study, but these results were not significantly different from those in our primary analyses. Also, self-reported adherence was a significant, independent predictor of viral suppression in our study, which provides a measure of validity for this assessment. Second, adherence measures have not been specifically validated for use with subjects who have low health literacy. While it is possible that systematic bias could be introduced as a result, the central findings were concordant with models of HIV-RNA suppression, an outcome that is not susceptible to such bias. Third, it is possible that the results are because of important factors or interactions not introduced into regression models. It is unlikely, however, that residual confounding plays a significant role in these analyses as the parameter estimates and trends remained remarkably stable across all models. Fourth, health literacy was defined by the 66-word REALM, which is merely a word pronunciation test. While the REALM is the most commonly used tool to measure literacy in the medical literature and correlates well with other established health literacy and basic literacy instruments ($r=.84$ to $.97$), a more comprehensive test of health literacy might have provided different results.[4,7] Fifth, HIV-RNA levels used in this analysis and assessment of adherence were not conducted concurrently. While this is not an optimal approach to evaluating the relationship between adherence and HIV-RNA suppression, adherence data likely reflect subjects' general behavior. Sixth, the generalizability of these findings may be limited owing to the fact that the cohort includes patients with a history of alcohol problems. Finally, it is possible that the subjects with low literacy may have received additional support in some fashion because of recognition of their vulnerability. While this is possible, the clinical staff was not informed of the subjects' health literacy status and providers do not readily discern which of their patients have low health literacy.[57,58]

CONCLUSION

Contrary to our hypothesis and prior observational reports, in this longitudinal cohort of HIV-infected patients with a history of alcohol problems, subjects with low health literacy had a consistent trend toward higher odds of adherence and virologic suppression. Although these trends were not statistically significant in all analyses, the counterintuitive findings presented in this paper underscore the need to pursue a fuller understanding of the mechanisms by which literacy affects health outcomes.

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